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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/770,639	SANCHEZ-MADRID ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56,59,60,67-77 and 105-108* is/are pending in the application.

4a) Of the above claim(s) *70-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56,59,60,67-69 and 105-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-18-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment to the specification and claims of May 18, 2007 is acknowledged.

   Claims 1-55, 57, 58, 61-66 and 78-104 are canceled.

   Claims 56, 59, and 105 are amended.

   Claims 56, 59, 60, 67-77 and 105-108 are pending.

   Claims 56, 59, 60, 67-69 and 105-108 are under consideration as they read on a method of treating an unwanted immune response comprising administering a depleting anti-CD69 antibody, wherein the species of unwanted immune response is "rheumatoid arthritis".

   Claims 70-77 have been withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being directed to non-elected inventions.

2. This Office Action is in response to applicant's amendment filed May 18, 2007.

   The previous objection to the specification has been withdrawn in view of applicant's amendments to the specification.

   The previous rejection under 35 U.S.C. § 112, 2nd paragraph has been withdrawn in view of applicant's amendment to the claims.

   The previous rejection under 35 U.S.C. § 112, 1st paragraph has been withdrawn in view of applicant's amendment to the claims.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

   > (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 56, 59, 60, 67-69, 105 and 106-108 stand rejected under 35 U.S.C. 103(a) as being unpatentable over McInnes et al. #1 (Immunol Today. 1998 Feb;19(2):75-9), in view of Ledbetter et al. (US 2003/0118592) and McInnes et al. #2 (Nat Med. 1997 Feb;3(2):189-95),

as evidenced by newly cited references

Feng et al. (Int. Immunol. 2002 Jun;14(6):535-44, cited on applicant's IDS of May 18, 2007), Nakayama et al. (J. Immunol. 2002 Jan 1;168(1):87-94, cited on applicant's IDS of May 18, 2007), Lauzurica et al. (Blood. 2000 Apr 1;95(7):2312-20, cited on applicant's IDS of May 18, 2007) and Cheon et al. (Clin. Exp. Immunol. 2002 Mar;127(3):547-52, cited herewith).

It should be noted that the newly cited evidentiary references are provided in direct response to applicant's introduction of new references in an attempt to show that one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the claimed invention in view of the knowledge and skill in the art, and in direct response to applicant's attempt to overcome *prima facie* unpatentability in view of allegedly unexpected results.

Applicants argues the instant claims are not obvious over the applied references for the following reasons:

- Applicant alleges the Examiner is using an impermissible obvious to try standard;
- Applicant alleges there is no motivation to combine the reference teachings; and
- Applicant alleges no reasonable expectation of success and unexpected results.

"Obvious to try"

Applicant argues the applied references present numerous choices to be tried but do not lead one of ordinary skill in the art to the claimed method of treatment. In particular, "[a]pplicants assert that a person having ordinary skill in the art, reviewing the combination of McInnes #1, Ledbetter, and McInnes #2 would have to try each of numerous choices until he or she possibly arrived at a successful result."

Applicant's argument has been considered but has not been found convincing.

Applicant is overstating the number of potential therapeutic avenues that one of ordinary skill in the art would have to choose from upon consideration of the applied references.

The McInnes references teach, in essence, that IL-15 mediates the recruitment and activation of T cells from the peripheral blood in rheumatoid arthritis patients, that said IL-15 activated T cells rapidly upregulate CD69 expression, that these $CD69^+$ T cells produce TNF-α and induce TNF-α production in monocytes/macrophage and that anti-CD69 antibodies block IL-15 activated T cell production/induction of TNFα in macrophage/monocytes. Whether blocking IL-15 ligand, IL-15 receptor or CD69, or depleting the IL-15 recruited T-cells that produce/induce the production of TNFα from macrophage, the reference teachings point one of ordinary skill in the art to three targets: the IL-15 ligand, the IL-15 receptor and CD69. Thus the applied references teach a limited number of therapeutic possibilities, any one of which would be predicted by one of ordinary skill in the art to useful in treating rheumatoid arthritis.

Applicant further points out that neither of the McInnes references contain animal study data and argues that "none of applied references teaches a specific depleting anti-CD69 antibodies, or shows any evidence of their efficacy in any context."

Applicant's argument has been considered but has not been found convincing.

First of all it is not the case that none of the references teach "specific depleting anti-CD69 antibodies".

As essentially stated in the prior Office Action of February 5, 2007, Ledbetter teaches human and humanized anti-CD69 antibodies with enhanced antibody dependent cell cytotoxicity and complement fixation activity, both of which lead to effective depletion of immune cells, such as B cells and T cells, that radiolabeled antibodies and toxin conjugated antibodies are effective for treating tumors, such as B cell tumors. As would be well known to one of ordinary skill in the art, radiolabeled antibodies and toxin conjugated antibodies deplete the cells to which they bind by killing them. Ledbetter further teaches that autoreactive T and B cells are present in rheumatoid arthritis patients, and claims various depleting antibodies, including anti-CD69 antibody, can be used to treat various autoimmune diseases and tumors, including rheumatoid arthritis.

Secondly, the applied references need not show evidence of depleting anti-CD69 antibodies in an animal model in order to render the claimed invention unpatentable. Rather, they only need provide sufficient teachings such that a method of treating rheumatoid arthritis with depleting anti-CD69 antibodies would have been obvious to one of ordinary skill in the art, and that one of ordinary skill in the art would have been assured of a reasonable expectation of success in practicing the claimed invention. The Examiner submits that the reference teachings meet this burden, essentially for the reasons stated above and the previous Office Action of February 5, 2007.

"Motivation to Combine"

Applicant argues, in essence, that the Examiner has failed to establish a prima facie case of obviousness since, according to applicant, the cited references, "do not provide either explicit or implicit motivation to combine...to arrive at the claimed invention." Applicant cites a U.S. Patent and Trademark Office memorandum following the Supreme Court decision on KSR Int 'l Co. v. Teleflex Inc. in support of this statement.

Applicant's argument has been considered but has not been found convincing, essentially for the reasons of record.

As essentially stated in the previous Office Action of February 5, 2007, one of ordinary skill would have been motivated to use the depleting anti-CD69 antibody of Ledbetter to treat rheumatoid arthritis because Ledbetter teaches that T cells are involved in rheumatoid arthritis and because McInnes teaches that CD69 expressing T cells are localized to the synovium of rheumatoid arthritis patients where they produce TNFα, a well known rheumatoid arthritis disease mediator, as taught by McInnes.

One of one of ordinary skill in the art would have been further motivated to use the depleting anti-CD69 antibody of Ledbetter to treat rheumatoid arthritis because such an antibody would be doubly effective in treating rheumatoid arthritis in that it would not only deplete $CD69^+$ T cells, but also for those CD69 T cells that are bound by the anti-CD69 antibody but resist depletion, the anti-CD69 antibody would, at the very least, prevent CD69 expressing T cells from inducing TNFα production in macrophage, as taught by McInnes #2 .

While applicant is correct in their assertion that neither McInnes #1 nor McInnes #2 explicitly teach the use of depleting anti-CD69 antibodies to treat rheumatoid arthritis, these references provide more than enough implicit motivation for one of ordinary skill in the art to make and use the depleting anti-CD69 antibody of Ledbetter to treat rheumatoid arthritis for the reasons given above.

In this regard, it should be noted that according to KSR Int 'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007), in an obvious analysis, "[t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art." In this regard, it is noted that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton," and "[a] court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." Id.

Furthermore, obviousness is viewed through the lens of a person of ordinary skill in the art with consideration of common knowledge and common sense. Dystar Textilfarben GMBH & Co. Deutschland KG v. C.H.Patrick Co., 464 F.3d 1356, 1367, 80 USPQ2d 1641, 1650 (Fed. Cir. 2006).

Reasonable expectation of success and unexpected results

Applicant argues, in essence, that one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the claimed invention because the reference teachings do not "show any in vivo data from animal models of arthritis." Moreover, citing Sancho et al. as support (Trends Immunol. 2005 Mar;26(3):136-40, submitted by applicant as Exhibit B), applicant further argues, "[p]reviously, *in vivo* data had shown that constitutive expression of CD69 by T cells in transgenic mice was not associated with inflammatory conditions. Also, the antigen-specific responses in transgenic mice without CD69 expression did not reveal reduced T-cell activation. These *in vivo* findings contradicted *in vitro* findings showing that CD69+ T-cells were associated with inflammatory conditions."

Applicant concludes, "[t]hus...without any data on point of any kind, and previously published contradictory *in vivo* data, the teachings...provide no reasonable expectation of success to one of ordinary skill in the art."

Applicant's argument has been considered but has not been found convincing.

With respect to the lack of "in vivo data from animal models of arthritis" in the reference teachings, as stated above under the "obvious to try" heading, the McInnes #1, McInnes #2 and Ledbetter teachings need not show in vivo data in order to render the claimed invention unpatentable. Rather, they need only provide sufficient teachings to make a method of treating rheumatoid arthritis with depleting anti-CD69 antibodies obvious to one of ordinary skill in the art, and to provide one of ordinary skill in the art with a reasonable expectation of success in practicing said invention. The Examiner submits that the reference teachings meet this burden.

With respect to applicant's argument concerning the teachings of Sancho et al., an argument about "the reasonable expectation of success" that one of ordinary skill in the art would have had in practicing the claimed invention must address what one of ordinary skill in the art would have known about the claimed subject matter *at the time the invention was made*, not as of 2005 with the publication of Sancho et al., Trends Immunol. 2005 Mar;26(3):136-40. See MPEP § 2943.02.

Thus, to properly consider whether one of ordinary skill in the art would have a reasonable expectation of success in practicing the claimed invention *at the time the invention was made*, the teachings of McInnes #1 and #2, related to the proinflammatory role of CD69 expressing T cells in rheumatoid arthritis, must be weighed in view of the teachings cited by Sancho to support the contention that a proinflammatory role for CD69 is contradicted by other evidence in the prior art.

As essentially stated in the prior Office Action of February 5, 2007, McInnes #1 teaches that IL-15 mediates the recruitment and activation of T cells from the peripheral blood in rheumatoid arthritis patients. McInnes #1 further teaches that IL-15 activation of T cells from rheumatoid arthritis patients rapidly upregulates CD69 expression, and that these $CD69^+$ T cells produce TNF-α and induce TNF-α production in macrophage. McInnes #1 concludes that because IL-15 mediates T cell recruitment and activation in the synovial membrane, IL-15 is a novel target for neutralization with biological agents (see entire document, in particular page 76, box 1 and right column, 1st paragraph, Figure 2, and page 78, right column, "Therapeutic Implications").

McInnes #2 echoes the teachings of McInnes #1, specifically showing that anti-CD69 antibody blocks IL-15 activated T cell production/induction of TNFα in macrophage/monocytes (see entire document, in particular Introduction on pages 189-190 and page 192, right column, 1st paragraph and Discussion, pages 192-194).

The pre-invention date data cited by Sancho that supposedly contradicts the reference teachings are as follows:

In support of the statement that "*in vivo* data had shown that constitutive expression of CD69 by T cells in transgenic mice was not associated with inflammatory conditions," Sancho cites Feng et al. (Int. Immunol. 2002 Jun;14(6):535-44) and Nakayama et al. (J. Immunol. 2002 Jan 1;168(1):87-94).

Feng teaches that mice transgenic for CD69 under control of a T cell specific promotor and enhancer display a transgene dose dependent accumulation of mature single positive thymocytes in the thymus due to the failure of these cells to emigate to the periphery (see, in particular, Abstract and Discussion pages 541-543). The teachings of Nakayama appear to be basically cumulative with the teachings of Feng.

While it is true that Feng does not report any signs of overt inflammation in mice that have T cells which overexpress CD69, at the same time the teachings of Feng do not particularly contradict the teachings of McInnes #1 and McInnes #2 in that the McInnes references describe the expression of CD69 in ***human*** T cells, in particular in ***human*** T cells from ***rheumatoid arthritis patients***, while the teachings of Feng describe the biology of CD69 in ***transgenic T cells from mice*** that are otherwise genetically wildtype. Moreover, even if Feng had treated their CD69 transgenic mice with type II collagen to induce arthritis, any difference or lack thereof, between transgenic mice and wild-type mice would have been confounded by the fact that overexpression of CD69 traps T cells in the thymus.

Similarly, in support of the statement that "antigen-specific responses in transgenic mice without CD69 expression did not reveal reduced T-cell activation," Sancho cites Lauzurica et al. (Blood. 2000 Apr 1;95(7):2312-20).

Lauzurica teaches that CD69 knock-out mice don't have an impaired response to a T cell antigen or impaired responses to thymus dependent or independent antigens (see entire document, in particular pages 2316-2318 and Discussion on pages 2318-2319).

However, Lauzurica does not particularly contradict the teachings of McInnes #1 and McInnes #2 references. The McInnes references teach that there is no consistent data in support of a single antigen driven process in rheumatoid arthritis synovial inflammation, and that IL-15 recruitment and activation of T cells, which includes upregulation of CD69 on the recruited T cells, can initiate and sustain the production of inflammatory mediators, such as TNFα, ***in the absence of antigen driven T cell activation***. (See, for example McInnes #1, in particular, page 75, Introduction on the left and right columns; page 77, left column, 1st paragraph to paragraph bridging page 77-78; and page 78, right column, first paragraph).

Thus, the lack of an effect on T cell response to antigens and humoral response in CD69 knock-out mice does not appear to be entirely relevant to the antigen-independent, CD69 expressing T cell mediated production and induction of TNFα from monocytes/macrophage in the synovial joint of human rheumatoid arthritis patients as taught by McInnes.

Therefore, when the McInnes #1 and McInnes #2 references as well as the references cited by Sancho in support of their statements that allegedly contradict the McInnes teachings are considered in their totality, the Examiner submits that one of ordinary skill in the art, by a preponderance of evidence, would have had a reasonable expectation of success in practicing the claimed invention.

Applicant further argues that "[t]he specification teaches, unexpectedly from the standpoint of one of ordinary skill in the art at the time the invention was made, that it is important that the CD69 specific antibody be a depletor of CD69+ cells, as opposed to specifically binding to CD69, while not depleting CD69+ cells. Treatment of CIA induced mice with mAb 2.2, a CD69 specific antibody that does not deplete CD69+ cells *in vivo,* exacerbated CIA in those mice. Treatment of CIA induced mice with mAb 2.3, a CD69 specific antibody that depletes CD69+ cells, significantly reduced CIA. Thus, the antibodies of McInnes #2 may actually exacerbate rheumatoid arthritis if they do not deplete CD69+ cells. This result was unexpected in light of McInnes #1, Ledbetter, and McInnes #2 and also other previously published *in vivo* data. Thus, Applicants submit that the methods of claims 56-60, 67-69 and 105-108 are based on unexpected properties and thus are non-obvious over McInnes #1, Ledbetter, and McInnes #2."

Applicant's argument has been considered but has not been found convincing.

Applicant's discovery that an anti-CD69 antibody that leads to the complete loss of CD69 expression on CD69 expressing cells but does not deplete said cells in vivo exacerbates murine collagen induced arthritis, while a depleting anti-CD69 antibody treats murine collagen induced arthritis, while surprising in the context of murine collagen induced arthritis, does not necessarily make the claimed invention surprising or unexpected.

First, it should be pointed out that McInnes #1 teaches that "T-cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious." (see, in particular, sentence bridging pages 77-78). Thus, McInnes specifically directs one of ordinary skill in the art to a therapy that *not only blocks T-cell activation but also depletes T cells* from the synovial compartment *as being most efficacious*.

Moreover, applicant's "unexpected results" argument is based on the assumption that one of ordinary skill in the art would generalize applicant's teachings about the different effects of anti-CD69 down-modulating vs anti-CD69 depleting antibodies in murine collagen induced arthritis to human rheumatoid arthritis. However, it is far from certain that applicant's unexpected results in murine collagen induced arthritis would necessarily hold true in human rheumatoid arthritis.

For example, Cheon et al. (Clin. Exp. Immunol. 2002 Mar;127(3):547-52) teaches that "TGF-β exerts diverse and even opposite effects depending on the cell types and conditions. In the present study, we provided evidence that TGF-β1 could contribute to the inflammation and progression of the disease in RA and OA." (See entire document, in particular, Introduction and Discussion on pages 547 and 551, including page 551, left column, 2nd paragraph).

Moreover, it should be noted that murine collagen-induced arthritis, may be, by definition, different from human rheumatoid arthritis in that *even in the absence of a disease inducing antigen*, cytokines such as IL-15, and associated IL-15-upregulated T cell surface molecules such as CD69, can initiate and sustain the production of inflammatory mediators, such as TNFα, as underscored by the teachings of McInnes #1 and #2 put forth above.

In conclusion, when Applicant's arguments and objective evidence, and the data in the instant specification are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentabililty, the instant claims, by a preponderance of evidence, remain unpatentable over McInnes #1 in view of Ledbetter and McInnes #2 as evidenced by Feng, Nakayama, Lauzurica and Cheon. See M.P.E.P. § 716.01(d).

5. No claim is allowed.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
August 5, 2007

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

08/05/07